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Synthesis of New Oxazolam Analogues as the Anti-anxiety Drugs

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Abstract

In this research, an efficient synthesis of oxazolam analogues with a number of advantages such as fast and cheap production procedure with great yields was presented. The purpose of this investigation was to develop a more economical and technically more feasible route to synthesis of oxazolam analogues. Aminobenzophenone was acylated to give corresponding amides. The ring forming reaction of amides with the appropriate amino (alcohol or thiol) produced oxazolam analogues with 83-98 % total yield.The structures of synthesized compounds were characterized by recording their IR, ^{1}H NMR, ^{13}C NMR, and mass spectra.

Keywords: Benzodiazepines,Oxazolam analogues, Tricyclic compounds.

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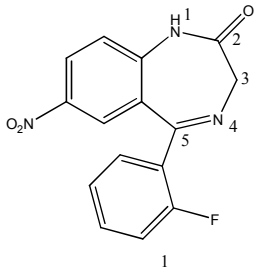
Introduction

Benzodiazepines have extensive drug effects and are most commonly used in psychiatry [1]. Among them, some of the imidazobenzodiazepines or 1,4-benzodiazepines are formed of three rings welded together exhibit biological activity. These series of therapeutic agents have shown their role in blocking a prominent place on GABA receptors in CNS [2-3].Benzodiazepines are also valuable intermediates for synthesizing fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furano-benzodiazepines [4-8]. Owing to their wide range of biological activity, these compounds and their synthesis procedures have received much attention. Benzodiazepines are synthesized by the condensation of *o*-phenylenediamines with unsaturated carbonyl compounds, haloketones, or ketones. The condensation process was done utilizing numerous reagents such as boron trifluoride diethyl etherate [9], polyphosphoric acid [10], $NaBH_4$ [11], SiO_2, $MgO/POCl_3$ [12], $Yb(OTf)_3$ [13], and acetic acid by applying microwave treatment [14]. Diazepam and chlorodiazepam were discovered more than thirty years ago. Since then, several new benzodiazepines have been identified to treat a broad variety of clinical disorders. They are utilized as anticonvulsants, hypnotics, and muscle relaxants with various duration of action. Lately, a novel generation of benzodiazepines belonging to the triazolobenzodiazepines class, such as triazolam and estazolam, has attained extensive use owing to their potent action at low doses. They are also frequently abused for suicidal and criminal purposes [15-20]. Here, the 4,5-double bond of desmethylflunitrazepam **1** (Scheme 1) was modified by addition of another ring to this system to produce nitroxazolam derivatives as oxazolam analogues.



1

Scheme 1. Structure of desmethylflunitrazepam.

Experimental

Apparatus and Reagents

All chemical compounds and solvents were received from usual commercial suppliers and used without further purification. The ^1H NMR spectra of materials were obtained using a JEOL 250 MHz NMR spectrometer utilizing TMS as an internal standard in $CDCl_3$. ^{13}C NMR spectra were obtained at 62.8 MHz with the same instrument. FT-IR spectra of all the final products were

acquired with a Nicolet Nexus 670 instrument using the KBr self-supported pellet technique. Uncorrected measurement of melting points was done on a Yanagimoto or a Büchi B-545 melting point apparatus.

*Synthesis of 2-(2-bromoacetamido)-5- nitro-2′-flourobenzophenone (**3**)*

At room temperature, 2.3 mmol bromoacetyl bromide was added dropwise to a solution of 2-amino-5-nitro-2′-flourobenzophenone (2 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stired for 4 h at 25 °C followed by addition of 30 mL ammonia solution 5%, which quenched the reaction solution. Then, the extraction step was performed with CH_2Cl_2 (2 × 25 mL).The combined organic layers were dried ($MgSO_4$), concentratedin vacuo and theresulting white product was further purified by washing with diethyl ether and cold methanol (yields 96 %). Yield: (96 %); white solid.IR (V_{max}, KBr): 1345, 1510 cm^{-1} (-NO_2), 1642, 1692 cm^{-1} 2(C=O), 3215 cm^{-1} (N-H). ^{1}HNMR (250 MHz, $CDCl_3$, δ/ppm): 4.08 (s, 2H), 7.19-7.38 (m, 2H), 7.55-7.66 (m, 2H), 8.43-8.46 (m, 2H), 8.95 (d, 1H, $^3J_{H-H}$=7.5), 12.16 (s, 1H). ^{13}CNMR (62.5 MHz, $CDCl_3$, δ/ppm): 43.2, 116.6, 116.9, 121.2, 123.1, 125.0, 125.1, 125.8, 126.0, 127.5, 129.0, 129.1, 129.8, 130.6, 130.7, 134.2, 134.6, 134.8, 142.4, 144.6, 157.6, 161.6, 166.2, 195.2.

*General procedure for the synthesis of **(5a-f)***

At room temperature, 2 mmol amino (alcohol or thiol) or diamine was added dropwise to a solution of 2-acetanilid-5-nitrobenzophenone (2 mmol) in EtOH (10 mL). The reaction mixture was stirred for 24 h at the reflux temperature. Afterward, the solvent removal was performed under reduced pressure and the residue separation was done by column chromatography (silica gel, Merck 230–400 mesh) using n-hexane–ethyl acetate (5:95) as eluent.

(4s)-3-((1's,2's)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)-4-phenyl oxazolidine-2-one (5a)

Yellow oil (98 %); IR (KBr) (υ_{max}, cm^{-1}): 1670 (C=O), 3432 (NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.50 (2H, t, CH_2, $^3J_{H-H}$ = 7.5), 3.20 (2H, t, CH_2 $^3J_{H-H}$= 7.5), 4.69 (2H, s, CH_2), 6.90 (1H, d, CH, $^3J_{H-H}$ = 7.5), 7.22 (1H, t, CH, $^3J_{H-H}$ = 7.5), 7.35 (1H, t, CH, $^3J_{H-H}$ = 7.5), 7.52 (1H, m, CH), 8.11 (1H, dd, CH), 8.37 (2H, d, CH, $^3J_{H-H}$ = 7.5). ^{13}CNMR (75.1 MHz, $CDCl_3$); 56.1, 60.4, 62.6, 115.8, 116.1, 116.4, 116.6, 117.0, 122.5, 122.8, 124.9, 126.1, 126.5, 129.1, 129.3, 131.3, 131.4, 136.3, 146.3, 154.6, 156.6, 159.9, 171.3. MS (m/z): 465 (M^+).

(4s)-3-((1's,2's)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)-4-phenyl oxazolidine-2-one (5b)

Yellow oil (98 %); IR (KBr) ($\tilde{\upsilon}_{max}$, cm^{-1}): 1675 (C=O), 3402 (NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.11 (2H, m, CH_2), 2.50 (2H, t, CH_2, $^{3}J_{H-H}$ = 7.6), 3.75(2H, t, CH_2, $^{3}J_{H-H}$ = 7.6), 4.90 (2H, s, CH_2), 6.95 (1H, d, CH, $^{3}J_{H-H}$ = 7.5), 7.23 (1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.37 (1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.55 (1H, m, CH), 8.11 (1H, dd, CH), 8.37 (2H, d, CH, $^{3}J_{H-H}$ = 7.5). ^{13}CNMR (75.1 MHz, $CDCl_3$); 25.6, 55.1, 59.3, 61.6, 115.8, 116.1, 116.4, 116.6, 117.0, 122.5, 122.8, 124.9, 126.1, 126.5, 129.1, 129.3, 131.3, 131.4, 136.3, 146.3, 154.6, 156.6, 159.9, 171.3. MS (m/z): 479 (M^{+}).

(4s)-3-((1's,2's)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)-4-phenyl oxazolidine-2-one (5c)

Yellow oil (97 %), IR (KBr) ($\tilde{\upsilon}_{max}$, cm^{-1}): 1685 (C=O), 3230 (NH), 3432 (NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.50 (2H, t, CH_2, $^{3}J_{H-H}$ = 7.6), 3.20 (2H, t, CH_2, $^{3}J_{H-H}$ = 7.6), 4.69 (2H, s, CH_2), 6.90 (1H, d, CH, $^{3}J_{H-H}$ = 7.5), 7.22 (1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.35 (1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.52 (1H, m, CH), 8.11 (1H, dd, CH), 8.37 (2H, d, CH, $^{3}J_{H-H}$ = 7.1). ^{13}CNMR (75.1 MHz, $CDCl_3$); 56.1, 60.4, 62.7, 115.8, 116.1, 116.4, 116.6, 117.2, 122.5, 122.9, 124.9, 126.1, 126.5, 129.1, 129.2, 131.3, 131.4, 136.2, 146.3, 154.7, 156.6, 159.8, 171.3. MS m/z: 464 (M+).

(4s)-3-((1's,2's)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)-4-phenyl oxazolidine-2-one (5d)

Yellow oil (98 %); IR (KBr) ($\tilde{\upsilon}_{max}$, cm^{-1}): 1675 (C=O), 3239 (NH), 3416 (NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.11 (2H, m, CH_2), 2.50 (2H, t, CH_2, $^{3}J_{H-H}$ = 7.1), 3.75 (2H, t, CH_2,$^{3}J_{H-H}$ = 7.1), 4.90 (2H, s, CH_2), 6.95 (1H, d, CH, $^{3}J_{H-H}$ = 7.6), 7.23 (1H, t, CH, $^{3}J_{H-H}$=7.5), 7.37(1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.55 (1H, m, CH, $^{3}J_{H-H}$ = 7.5), 8.11 (1H, dd, CH), 8.37 (2H, d, CH, $^{3}J_{H-H}$ = 7.5). ^{13}CNMR (75.1 MHz, $CDCl_3$); 25.6, 56.1, 60.4, 62.7 115.8, 116.1, 116.4, 116.6, 117.0, 122.5, 123.1, 124.9, 126.2, 126.5, 129.2, 129.3, 131.2, 131.4, 136.3, 146.3, 154.6, 156.6, 159.9, 171.3. MS (m/z): 421 (M+).

(4s)-3-((1's,2's)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)-4-phenyl oxazolidine-2-one (5e)

Yellow oil (94 %); IR (KBr) ($\tilde{\upsilon}_{max}$, cm^{-1}): 1678 (C=O), 3431 (NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.52 (2H, t, CH_2, $^{3}J_{H-H}$ = 7.6), 2.92 (2H, t, CH_2, $^{3}J_{H-H}$ = 7.6), 4.68 (2H, s, CH_2), 6.91 (1H, d, CH, $^{3}J_{H-H}$ = 7.5), 7.22 (1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.37 (1H, t, CH, $^{3}J_{H-H}$ = 7.5), 7.52 (1H, m, CH, $^{3}J_{H-H}$ = 7.5), 8.14 (1H, dd, CH), 8.33 (2H, d, CH, $^{3}J_{H-H}$ = 7.1), ^{13}CNMR (75.1 MHz, $CDCl_3$); 56.2, 53.3, 62.7,

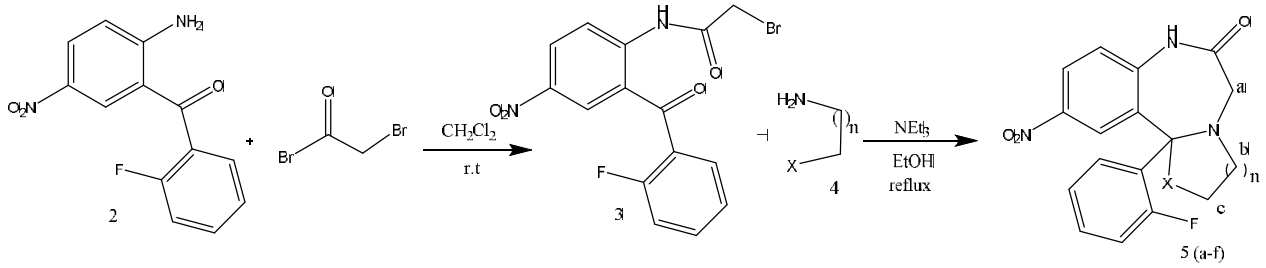
115.8, 116.3, 116.4, 116.7, 117.0, 122.5, 122.8, 124.7, 126.2, 126.5, 129.1, 129.3, 131.3, 131.4, 136.3, 146.3, 154.6, 156.6, 159.9, 171.2. MS (m/z): 481 (M^+).

(4s)-3-((1's,2's)-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)-4-phenyl oxazolidine-2-one (5f)

Yellow oil (92 %); IR (KBr) ($\tilde{\upsilon}_{max}$, cm^{-1}): 1679 (C=O), 3422 (NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 2.13 (2H, m, CH_2), 2.41 (2H, t, CH_2, $^3J_{H-H}$ = 7.5), 3.55 (2H, t, CH_2, $^3J_{H-H}$ = 7.5), 4.90 (2H, s, CH_2), 6.95 (1H, d, CH, $^3J_{H-H}$ = 7.5), 7.23 (1H, t, CH, $^3J_{H-H}$=7.5), 7.37 (1H, t, CH, $^3J_{H-H}$ = 7.5), 7.55 (1H, m, CH), 8.11 (1H, dd, CH), 8.37 (2H, d, CH, $^3J_{H-H}$ = 7.5), ^{13}CNMR (75.1 MHz, $CDCl_3$); 24.9, 49.8, 60.3, 62.9, 115.9, 116.2, 116.4, 116.7, 117.1, 122.5, 122.8, 124.8, 126.1, 126.5, 129.1, 129.3, 131.3, 131.4, 136.3, 146.3, 154.6, 156.6, 159.9, 171.3. MS (m/z): 495 (M^+).

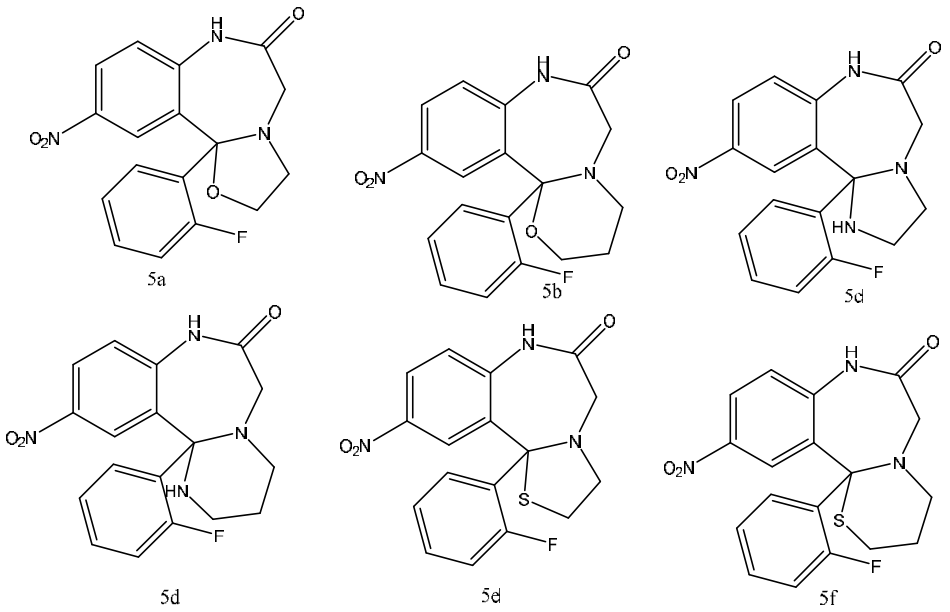
Results and discussion

In this research, a comfortable and scalable method for the synthesis of oxazolam analogues is presented, scheme 2.



Scheme 2. The synthesis pathway for **5(a-f)** production.

Oxazolam analogues **(5a-f)** were synthesized as shown in scheme 3. In the first step, the benzodiazepine nucleus (**5**) was synthesized according to Morales et al. report [11]. The process started with treatement of 2-amino-5-nitro-2′-flourobenzophenone (**2**), a commercially acceccible compound, with bromoacetyl bromide in dichloromethane to produce the intermediate, 2-(2-bromoacetamido)-2′-flourobenzophenone (**3**), in good yield (96 %). One-pot cyclization of (**3**) in ethanol was carried out under reflux in the presence of appropriateamino (alcohol or thiol) (**4**) and triethylamine as base. Oxazolam analogues **(5a-f)**were obtained in high total yield (83-98 %) as the only isomer were shown by TLC analysis.

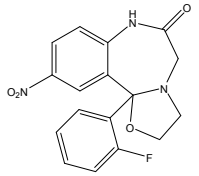
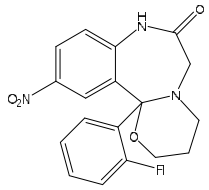
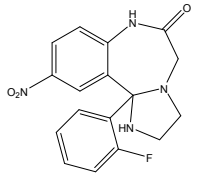
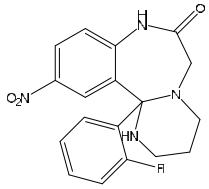
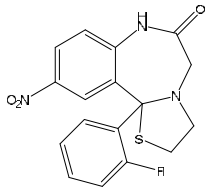
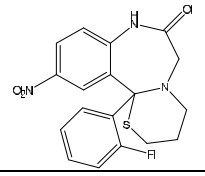


Scheme 3. Structures of synthesized oxazolam analogues.

Other derivatives of substrate were examined. The results are summarized in Table **1**, which show that the creation of a five-membered ring has a better yield than a six-membered ring, that can reflect the greater stability of the five-membered cycles. The tendency for ring formation has also increased with increasing heteroatom nucleophilicity from oxygen to nitrogen and sulfur. As a result, the yield of sulfur-containing rings has increased.

The structures charactrization of cycloaddition products were performed by ^{1}H NMR and ^{13}C NMR. The appearance of a triplet signal with $^{3}J_{HH}$ of about 7 Hz in the ^{1}H NMR spectra of **5** originates from a new ring formation. For example, the ^{1}H NMR spectrum of **5a** exhibits a triplet signal at δ = 2.50 ppm, a triplet at δ = 3.20 and a singlet at δ = 4.69 ppm which are related to H*b*, H*c* and H*a* protons, respectively. Also ^{13}C NMR showed signals corresponding to three (CH_2) carbons that were directly bonded to H*b*, H*c* and H*a* in the region of 56.1, 60.4 and 62.7 ppm, respectively.

Table 1. Yield of oxazolam analogues (5a-f).

Entry	X	Product	Time (h)	n	yield
1	OH		24	0	85
2	OH		24	1	83
3	NH_2		24	0	95
4	NH_2		24	1	93
5	SH		24	0	98
6	SH		24	1	92

Conclusions

A preferable and new method was illustrated for the synthesis of oxazolam analogues.The total synthesis of oxazolam analogues under mentioned conditions was accomplished with 83-98 % yield. Results revealed the greater yield for the creation of a five-membered ring than a six-membered ring confirming the probable greater stability of the five-membered cycles. The developed synthesis method proposes several advantages of short reaction times, high yields, mild condition, simplicity, and easy workup compared to the other conventional methods of synthesis.

Acknowledgment

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